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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,155	04/08/2004	Tibor Sipos	TS-008(CIP)	9572

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The Law Office of Imre Balogh
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EXAMINER	
HANLEY, SUSAN MARIE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,155	SIPOS ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-48 are presented for examination.

DETAILED ACTION

Claim Objections

Claims 8-21 and 28-41 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 8-21 and 28-41 provide the structural formulae for the compounds that are named in the claims from which they depend. The name of the compound is equivalent to its structure. Therefore, providing the structure of the compound does not limit the parent claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42, and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,750,104 ('104) in view of Sherman et al (2000; cited in the IDS filed 4/8/04).

'104 claims a composition comprising an enzyme/buffer mixture and a method of using said composition for treating digestive enzyme deficiency, digestive disorders, and so on. The claimed composition comprises about 10 to 70% of pancreatic enzymes such as proteases, lipases, amylase, and

the like, about 0.5 to 16% of a disintegrant, about 1-19% of an adhesive polymer, about 7.0 to 19% of a non-porous, gastric acid-resistant polymer coating, ad 45-60% of a buffering agent.

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42, and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,324,514 (cited in the IDS filed 4/8/04; '514) in view of Sherman et al (2000). '514 claims a composition comprising an enzyme/buffer mixture and a method of using said composition for treating a digestive enzyme deficiency, digestive disorders, and so on. The claimed composition comprises about 71 to 90% of pancreatic enzymes such as proteases, lipases, amylase, and the like, about 0.3-13% of a bile salt, about 0.9 to 16% of a disintegrant, about 0.3-15.0% of an adhesive polymer, about 7.0 to 15% of a non-porous, gastric acid-resistant polymer coating, and 0.8% to 5.0% of a buffering agent.

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42, and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,460,812 ((cited in the IDS filed 4/8/04; '812) in view of Sherman et al (2000). '812 claims a composition comprising an enzyme/buffer mixture and a method of using said composition for treating a digestive enzyme deficiency, digestive disorders, and so on. The claimed composition comprises about 10 to 90% of pancreatic enzymes such as proteases, lipases, amylase, and the like, about 0.3-75% of a bile salt, about 0.9 to 16% of a disintegrant, about 0.3-15.0% of an adhesive polymer, about 7.0 to 15% of a non-porous, gastric acid-resistant polymer coating, and 7.3% to ? of a buffering agent. The claim does not have an end value for this range. Using the specification, the composition comprises from 5-40% or a buffering agent (col. 6, line 1).

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42, and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,578,304 ((cited in the IDS filed 4/8/04; '304) in view of Sherman et al (2000). '304 claims a composition comprising an enzyme/buffer mixture and a method of using said composition for treating a digestive enzyme deficiency, digestive disorders, and so on. The claimed composition comprises about 10 to 90% of

pancreatic enzymes such as proteases, lipases, amylase, and the like, about 0.3-75% of a bile salt, about 0.9 to 16% of a disintegrant, about 0.3-15.0% of an adhesive polymer, about 7.0 to 15% of a non-porous, gastric acid-resistant polymer coating, and 7.35-40.5% of a buffering agent.

None of these patents teach an enzyme composition having identical combination for the concentrations of components as the instant application. None of the patents disclose using the claimed composition to treat PI-induced diarrhea or steatorrhea in HIV patients.

Sherman et al. teach that PI-induced diarrhea in an HIV patient can be treated with medicaments containing pancreatic enzymes. Viokase and Ultrase MT 20 were successful at reducing the incidence and symptoms of diarrhea (Table 1, p. 910). Sherman et al. describe diarrhea as a gastrointestinal complication of HIV (p. 908, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the pancreatic enzyme compositions claimed by '304, '812, '514 or '104 with the protease inhibitors to treat PI-induced diarrhea in HIV patients. All of these patents describe a composition having the same groups of components in ranges of concentration that overlap. Each group has some common members. Hence, the compositions claimed in the patents are obvious over the claimed composition because they disclose the same groups of components having overlapping ranges of concentration. Each of the patents claim that the claimed composition can be used to treat digestive disorders. Sherman describes diarrhea as a gastrointestinal complication. The broadest reasonable interpretation of disorder as an ailment that affects the normal function of the body. By that definition, it is reasonable to say that a disorder and a complication are equivalent. Sherman demonstrates two brands of medicaments having pancreatic enzymes. Both are effective for treating PI-induced diarrhea. Each the named patents claims medicaments comprising pancreatic enzymes for treating digestive disorders. The ordinary artisan would have been motivated to employ the compositions claimed in the named patents to treat PI-induced diarrhea because they contain pancreatic enzymes which have been successfully proven to treat diarrhea. The broadest reasonable interpretation of the term "composition" is a collection of items. The

administration of a PI inhibitor and any of the claimed compositions meets the limitation of a collection because the two medicaments are items that are together. Since medicaments containing pancreatic enzymes have been shown to be an effective treatment for PI-induced diarrhea, the ordinary artisan would have had a reasonable expectation that any of the claimed compositions could be used interchangeably to treat the ailment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and method for reducing diarrhea and steatorrhea in HIV patients and treating the effects of fat malabsorption and loss of body fat associated with diarrhea and steatorrhea in HIV patients, it does not reasonably provide enablement for preventing diarrhea or steatorrhea in HIV patients or treating the effects of fat malabsorption and loss of body fat associated with diarrhea and steatorrhea in HIV patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for reducing or preventing diarrhea or steatorrhea in an HIV patient undergoing treatment with protease inhibitors (PI) and for correcting treating the effects of fat malabsorption and loss of body fat associated with diarrhea and steatorrhea in HIV patients by administering a composition comprising pancreatic enzymes. The specification discloses that HIV-positive patients taking the claimed pancreatic composition responded positively in that they had fewer loose stools and reduced incidence of gastrointestinal distention and flatulence (page 27). However, there

is no disclosure related to the prevention of PI-induced diarrhea or steatorrhea in an HIV patient by the claimed composition. Nor is there disclosure that supports the correction, which is interpreted to mean the 100% reversal of the effects of fat malabsorption and loss of body fat associated with diarrhea and steatorrhea in HIV patients. The limited showing of reducing the symptoms and incidence caused by PI-induced diarrhea or steatorrhea in an HIV patient is not sufficient to enable a claim drawn to the prevention or correction of a disease that is unpredictable.

The specification does not disclose if one skilled in the art can utilize the claimed composition to prevent PI-induced diarrhea or steatorrhea in an HIV patient or correct the effects of fat malabsorption and loss of body fat associated with diarrhea and steatorrhea in HIV patients with a reasonable expectation of results. Sherman et al. (2000) report that diarrhea is a common complication in patients with HIV and can have a number of etiologies. Diarrhea associated with the use of PI's can be managed by the administration of one of the anti-diarrheals which are summarized in Table 1, page 910. Table 1 shows that there is success in reducing the incidence and symptoms of the malady. However, there is no report of prevention or correction of symptoms associate with the condition. Indeed, it would be difficult to show that a medicament is keeping a person from contracting or falling ill to a medical condition. Prevention is the reduction of the predisposition of an individual to a disease. "Predisposition" means to make someone inclined to favor something in advance. Likewise, it is difficult to correct, which is interpreted to mean the 100% reversal, of the effects of fat malabsorption and weight loss associated with HIV. The specification is enabled for reducing the diarrhea or steatorrhea associated with PI therapy for HIV patients. However, the specification does not teach how the skilled artisan would know in advance if someone were predisposed to the claimed conditions. Even if the skilled artisan did know if an individual was predisposed to contract diarrhea or steatorrhea induce by PI , it is unclear how the artisan would determine a reduction in the likelihood of a medical condition that and individual will contract or exhibit at some time in the future.

It is not clear if the results disclosed for the claimed method in the instant application can be extrapolated to the prevention of PI-associated diarrhea and steatorrhea. The specification shows only that the claimed composition is effective in reducing the symptoms and incidence caused by PI-induced diarrhea or steatorrhea in an HIV patient. Nor does the prior art support the notion that an anti-diarrheal can effectively prevent the symptoms and incidence caused by PI-induced diarrhea or steatorrhea in an HIV patient with any reliability. Hence the prevention of diarrhea or steatorrhea and the correction of the effects of fat malabsorption and weight loss in an HIV patient taking PI therapy is reduced to trial and error with potential medications because the prior art discloses that the skilled artisan, a medical doctor, cannot easily predict which medication will successfully prevent PI-induced diarrhea or steatorrhea and correct the effects of fat malabsorption and weight loss in an HIV patient. The instant specification does not fill this gap in knowledge. If the use of the claimed composition for preventing PI-induced diarrhea or steatorrhea and correcting the effects of fat malabsorption and weight loss in an HIV patient is not generally applicable, then claimed method would have to be considered on an individual basis for each HIV patient. Thus would be considered undue experimentation. Thus, claims 1-48 are not commensurate in scope with the enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 22, 26 and 44 recite the limitation "colipase" in part b) of both claims. There is insufficient antecedent basis for this limitation in the claim. In part b of both claims 1 and 7, the Markush group is phrased as "enzymes consisting of." Co-enzyme is a member of this group. The name of

"coenzyme" is a misnomer because coenzyme is a cofactor. Since is it is not an enzyme, it lacks antecedent basis in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 44, 45 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sipos (US 5,750,104) in view of Sherman et al. (2000).

The disclosure of Sipos is discussed *vide supra*. Briefly, Sipos discloses a buffered composition containing pancreatic enzymes, a disintegrant, an adhesive polymers and a non-porous, gastric acid-resistant polymer coating. The claimed concentration ranges overlap those of the instant claims. Sipos teaches that the composition can be used to treat digestive disorders.

Sipos does not teach that the disclosed composition can be used in combination with a protease inhibitor to treat PI-induced diarrhea or steatorrhea in HIV patients.

Sherman et al. teach that PI-induced diarrhea in an HIV patient can be treated with medicaments containing pancreatic enzymes. Viokase and Ultrase MT 20 were successful at reducing the incidence and symptoms of diarrhea (Table 1, p. 910). Sherman et al. describe diarrhea as a gastrointestinal complication of HIV (p. 908, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the pancreatic enzyme composition disclosed by '104 to treat PI-induced diarrhea in HIV patients. The ordinary artisan would have been motivated to do so because the composition disclosed by

'104 contains pancreatic enzymes which have been successfully proven to treat diarrhea. The broadest reasonable interpretation of the term "composition" is a collection of items. The administration of a PI inhibitor and the pancreatic enzyme composition meets the limitation of a collection because the two medicaments are items that are together. Since medicaments containing pancreatic enzymes have been shown to be an effective treatment for PI-induced diarrhea, the ordinary artisan would have had a reasonable expectation that any of the claimed composition could be used interchangeably with other pancreatic enzyme compositions to treat the ailment.

Regarding instant claims 43-48, drawn to a composition and method for correcting fat malabsorption and loss of body mass associated with diarrhea and/or steatorrhea, the treatment of diarrhea and/or steatorrhea will necessarily treat fat malabsorption and loss of body mass since diarrhea and/or steatorrhea are the cause of the associated symptoms.

Claims 1-6, 8-12, 22-26, 28-41, and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sipos (US 5,750,104) view of Sherman et al. (2000) as applied to claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 44, 45 and 48 above, and further in view of Stuyver (US 2003/0225029) and Hetherington et al. (US 2003/0096274).

The disclosure of Sipos is discussed *vide supra.*

Sipos does not teach that the composition or method of use thereof, comprises a protease inhibitor that is a nucleoside reverse transcriptase inhibitor, as in claim 3, or a non-nucleoside reverse transcriptase inhibitor, as in claim 4.

Stuyver teaches that lamivudine and didanosine are standard anti-viral agents for the treatment of AIDS and that both substances can cause diarrhea in the patient (p. 4-5, Table 2).

Hetherington et al. disclose that abacavir is a standard anti-viral treatment for AIDS but that it has gastrointestinal side effects that in include diarrhea (p. 2, section 0019 and p. 13, section 0116).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the composition disclosed by Sipos view of Sherman et al. to treat diarrhea or steatorrhea in HIV patients caused by a nucleoside reverse transcriptase inhibitor or a non-nucleoside reverse transcriptase inhibitor in employ. The ordinary artisan would have been motivated to do so because the antivirals in claims 3 and 4 are well known to cause diarrhea. The ordinary artisan would have wanted to take advantage of a composition having an HIV antiviral and an antidiarrheal agent in order to reduce the incidence or symptoms of medicaments that are well known to cause diarrhea. The ordinary artisan would have had a reasonable expectation that a compositions comprising HIV antivirals from other classes or a method of using such a composition could reduce the incidence of diarrhea caused by the PI of claims 3 or 4 because all of the disclosed and claimed anti-virals work by the same mechanism (protease inhibition). Hence, the etiology of the diarrhea side effects would be similar and the ordinary artisan could reasonably expect that diarrhea caused by other HIV protease inhibitors would respond to the same treatment comprising the claimed buffer/pancreatic enzymes.

Claims 1-3, 6-12, 22, 23, 26-32, 42-45 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sipos (US 5,750,104) in view of Sherman et al. (2000) as applied to claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 44, 45 and 48 above, and further in view of Canani et al. (1999) and Gaskin et al. (1982).

The disclosure of Sipos in view of Sherman is discussed *vide supra.*

The combined disclosures do not teach a composition or method of use thereof having colipase.

Canani et al. disclose a medication trial for children with HIV with the intention of improving gastrointestinal function that had been negatively affected by protease inhibitor therapy. Initially, 30% (3 out of 10 subjects) had steatorrhea due to fat over-excretion in the feces. Canani et al. administered ritonavir with the protease inhibitors to ameliorate the side effects. Ritonovir improves the pharmacokinetics of drug metabolized by cytochrome P450 monooxygenase.

Gaskin et al. disclose that the activity of pancreatic lipase in duodenal secretions from patients with and without steatorrhea can be altered by activating pancreatic lipase. Patients with steatorrhea initially had much less total lipase and colipase activity compared to normal subjects (Table II, page 432). Gaskin et al. found that they could increase the lipase activity by adding exogenous porcine colipase. Gaskin et al. disclose that the lipolytic activity from the samples of patients experiencing steatorrhea increased significantly after adding the porcine colipase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add colipase to a composition comprising the pancreatic enzyme composition taught by '104 in view of Sherman and to use the resulting medicament for the treatment of steatorrhea in HIV patients taking protease inhibitors. The ordinary artisan would have been motivated to do so because pancreatic lipases break down fat and colipase is a cofactor that increases the activity of lipase. The administration of a composition comprising colipase and pancreatic lipases in combination of PI therapy would serve to decrease the incidence of steatorrhea, the overexcretion of fat in the stool, is a known side effect of PI therapy. The broadest reasonable interpretation of the term "composition" is a collection of items. The administration of a protease inhibitor and the composition taught by '104 and colipase meets the limitation of a collection because the two medicaments are items that are together. The ordinary artisan would have had a reasonable expectation of success that the claimed composition comprising colipase could be used for treatment of PI-induced steatorrhea because pancreatic enzymes are known to breakdown fat and colipase has been shown to increase lipase activity.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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